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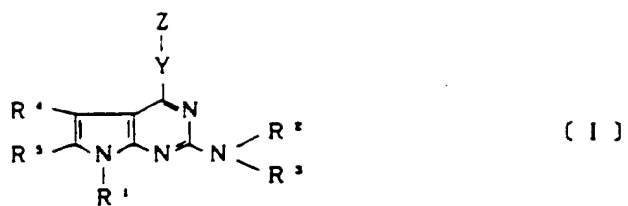
(54) **PYRROLO 2,3-d]PYRIMIDINE DERIVATIVE, PROCESS FOR PREPARING THE SAME, AND
PHARMACEUTICAL PREPARATION COMPRISING THE DERIVATIVE AS ACTIVE INGREDIENT.**

(57) A pyrrolo[2,3-d]pyrimidine derivative represented by general formula (1), wherein R¹ represents H or a hydrocarbon residue; R² and R³ each independently represent H a hydrocarbon residue or an acyl group, provided that R² and R³ may combine with a neighboring N atom to form a cyclic amino group; R⁴ and R⁵ each independently represent H, a halogen atom or an alkyl group; Y represents a linear or cyclic amino group bonding through an N atom with the pyrimidine ring; Z represents H, a hydrocarbon residue, an acyl group, a carboxyl group, a hydroxyl group, an alkoxycarbonyl group, an acyloxy group, an alkoxy group, an alkoxyminoalkyl group or an amino group, provided that Z may form in cooperation with Z a morpholino group or a thiomorpholino group.

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Applicants: **Arlindo L. Castelhana, et al.**
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Exhibit 66

Rank Xerox (UK) Business Services

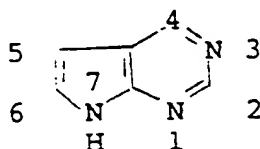


TECHNICAL FIELD

The present invention relates to a novel pyrrolo[2,3-d]pyrimidine derivative, a process for producing same, and a pharmaceutical preparation comprising the derivative, and more particularly, relates to a novel pyrrolo[2,3-d]pyrimidine derivative having independently a substituted or unsubstituted amino group at the 2- and 4- positions of the pyrimidine ring, a pharmaceutically acceptable acid addition salt thereof, a process for producing same, and a pharmaceutical preparation comprising same as an active ingredient; particularly, a pharmaceutical preparation useful for the treatment, i.e., prophylaxis and therapy, of hypoxemia associated with respiratory diseases.

BACKGROUND ART

Compounds having the pyrrolo[2,3-d]pyrimidine skeleton of the formula:



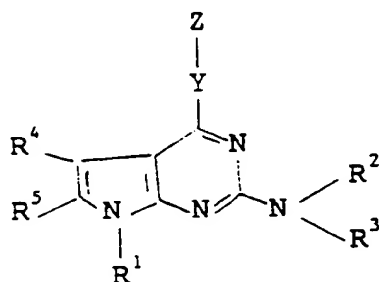
are known to have various important pharmacological actions. For example, it is known that antibacterial compounds are substituted by amino groups at both the 2- and 4- positions of the skeleton (see, U.K. Patent 812, 366, and Townsend L.B. et al, *J. Med. Chem.*, Vol. 31, 1501(1988), etc.). and that compounds useful as a herbicide and antibiotic have a primary amino group as the amino group (Okuda et al, *Nippon Noyaku-qakkaishi*, Vol. 6, 9(1981), Pedersen E.B. et al., *Chemica Scripta*, Vol. 28, 201(1988), etc.). Other known antiviral compounds have an amino group at the 2- and 4- positions as well as a sugar residue at the 7- position of the skeleton (e.g., E.P. Publication No. 57548).

Nevertheless, in particular, pyrrolo[2,3-d]pyrimidine derivatives having an alkyl or alkenyl group at the 7- position, an amino group substituted by alkyl or alkenyl group at the 2- position, and a cyclic amino or chain substituted amino group at the 4- position, have not been described in the prior art.

DISCLOSURE OF INVENTION

The present inventors made extensive and intensive research into pyrrolo[2,3-d]pyrimidine derivatives and a process for producing same, and as a result, surprisingly found that, of the compounds not disclosed in the prior art, those of the formula [I] described below are particularly, efficacious for the prophylaxis and therapy of hypoxemia associated with respiratory diseases. Note, in the treatment of hypoxemia, to this day it has not been known that a compound can suffice in the light of both the pharmaceutical effect and toxicity there.

Thus, in accordance with the present invention there are provided, pyrrolo[2,3-d]pyrimidine derivatives having the formula [I] described below, pharmaceutically acceptable acid addition salts thereof, a process for producing same, as well as pharmaceutical preparations containing same derivatives or salts as an active ingredient:



... [I]

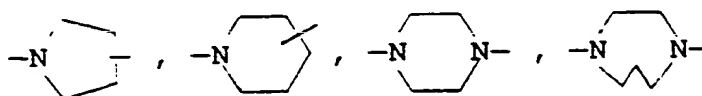
wherein

R¹ represents a hydrogen atom, or an unsubstituted or substituted alkyl, alkenyl or aralkyl group;

R² and R³, independently of each other, represent a hydrogen atom, or an unsubstituted or substituted alkyl, alkenyl, aralkyl or alkylcarbonyl group; or R² and R³ are optionally taken together with the adjacent nitrogen atom to form a cyclic amino group;

R⁴ and R⁵ independently of each other, represent a hydrogen atom, halogen atom, or an unsubstituted or substituted alkyl group;

Y is a linking group bonded to the pyrimidine ring via a nitrogen atom therein of the formula



or -N(G)-, wherein G represents a hydrogen atom or an alkyl group;

Z represents a group bonded to a carbon or nitrogen atom in the linking group, and is a hydrogen atom, an unsubstituted or substituted alkyl, alkenyl, aralkyl, aryl, alkylcarbonyl, arylcarbonyl or aralkylcarbonyl group; or represents a group bonded to a carbon atom in the linking group, and is a carboxyl, hydroxyl; or an unsubstituted or substituted alkyloxycarbonyl, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkyloxy, alkyloxyiminoalkyl group, or mono- or disubstituted alkyl- and/or alkylcarbonylamino group; or Y and Z are taken together to form morpholino or thio-morpholino group;

each substituent in said substituted group is substituted at a chain or cyclic moiety of the alkyl, alkenyl, aralkyl or aryl moiety, respectively, and represents an alkyl, halogenated alkyl, alkylcarbonyl, alkyloxy, alkylcarbonyloxy, hydroxyl, mono- or di-alkylamino, amino, morpholino, piperidino, nitro or cyano group, or a halogen atom;

with a proviso that R² and R³ do not represent a hydrogen atom at the same time, and that, when R¹ represents hydrogen atom, the combinations wherein one of R² and R³ represents a hydrogen atom and another represents an alkyl group are excluded:

BEST MODE OF CARRYING OUT THE INVENTION

This invention is disclosed in detail below.

An alkyl moiety of each group, unless defined otherwise, is herein intended to mean a C₁ - C₁₀ straight or branched chain aliphatic hydrocarbon residue, alicyclic hydrocarbon residue or chainaliphatic-alicyclic hydrocarbon residue, and is for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropyl-methyl, cyclobuthymethyl and the like; preferably a C₁ - C₆ lower alkyl group.

The term "alkenyl group" is intended to mean a C₂ - C₆ straight or branched chain aliphatic hydrocarbon residue containing one double bond, for example, allyl, 1-methylallyl, 2-methylallyl, 2-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 3-butenyl, 2-pentenyl, 3-methyl-2-pentenyl, 2-hexenyl, 3-cyclopropylallyl, 3-cyclopentenyl, 3-cyclohexenyl, and the like.

The term "aryl group" is intended to mean aromatic hydrocarbon cyclic groups or aromatic heterocyclic groups constructed of a mono-ring or fused ring and examples thereof include phenyl, 1-naphthyl, 2-naphthyl, 2-pyrrolyl, 2-furyl, 2-thienyl, 2-pyridyl and the like.

The term "aralkyl group" is lower aralkyl groups constructed of lower alkyl groups and aryl groups, and containing in total 6 to 20 carbon atoms, for example, benzyl, 1-phenylethyl, 1-methyl-1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, cinnamyl, diphenylmethyl (benzhydryl), triphenylmethyl, 1-naphthylmethyl, 1-(1-naphthyl)ethyl, 1,2,3,4-tetrahydronaphthyl-1-yl, 2-pyrrolylmethyl, 2-furfuryl, 2-thienylmethyl and the like.

The above-described alkyl, alkenyl, aryl and aralkyl groups may have a substituent in the chain moiety or cyclic moiety thereof, and examples of the substituent include alkyl groups having about 1 to 4 carbon atoms, halogenated alkyl, alkylcarbonyl, alkyloxy, alkylcarbonyloxy, hydroxyl, mono- or di- substituted alkylamino, amino, morpholino, piperidino, nitro and cyano groups, and halogen atoms, i.e., fluorine, chlorine, bromine or iodine atom, etc.. The groups defined below also may have the above-described substituents in the chain portion or cyclic portion thereof.

In the present invention, the term "alkylcarbonyl group", which is constructed of said lower alkyl and carbonyl group, is intended to mean C₂-C₇ lower alkylacyl groups, such as acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2-methylbutanoyl, 3-methylbutanoyl, pivaloyl, hexanoyl, cyclopropylcarbonyl, and the like.

The term "arylcarbonyl group" which is constructed of said aryl and carbonyl group, is intended to mean, for example, benzoyl, toluoyl, naphthoyl, 2-pyrrolicarbonyl, 2-furancarboxyl, 2-thiophenecarbonyl, and the like.

The term "aralkylcarbonyl group", which is constructed of said aralkyl and carbonyl group, is intended to mean C₇-C₁₉ aralkylcarbonyl groups, such as phenylacetyl, 3-phenylpropanoyl, 4-phenylbutanoyl, cinnamoyl, diphenylacetyl, naphthylacetyl, 2-pyrrolylacetyl, 2-furylacetyl, 2-thienylacetyl, and the like.

The term "alkyloxycarbonyl group", which is a carboxylic acid ester residue containing said alkyl group, is intended to mean C₂-C₇ lower alkyloxycarbonyl groups, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropylloxycarbonyl, butoxycarbonyl, tert-butyloxycarbonyl, cyclohexyloxycarbonyl, and the like.

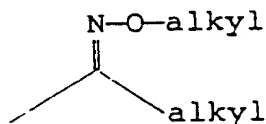
The term "alkylcarbonyloxy group" which is constructed of said alkylcarbonyl and oxy group, is intended to mean C₂-C₇ lower alkylcarbonyloxy groups, such as acetoxyl, propanoyloxy, butanoyloxy, 2-methylpropanoyloxy, pentanoyloxy, pivaloyloxy, hexanoyloxy, and the like.

The term "arylcarbonyloxy group", which is constructed of said arylcarbonyl and oxy group, is intended to mean, for example, benzoyloxy, toluoyloxy, naphthoyloxy, 2-pyrrolicarbonyloxy, 2-furancarboxyloxy, 2-thiophenecarbonyloxy, and the like.

The term "aralkylcarbonyloxy group", which is constructed of said aralkylcarbonyl and oxy group, is intended to mean lower aralkylacyloxy groups, such as phenylacetoxyl, 3-phenylpropanoyloxy, 4-phenylbutanoyloxy, cinnamoyloxy, 2-pyrrolylacetoxy, 2-furylacetoxy, 2-thienylacetoxy, and the like.

The term "alkyloxy group", which is constructed of said alkyl and oxy group, is intended to mean a C₁-C₆ lower alkyloxy group; such as methoxy, ethoxy, propoxy, butoxy, isopropoxy, sec-butyloxy, tert-butyloxy, pentyloxy, cyclopropyloxy, cyclopropylmethyloxy, cyclohexyloxy, and the like.

The term "alkyloxyiminoalkyl group" represents a group that, in the alkylcarbonyl groups, the oxygen atom is replaced with a group N-O-alkyl, and has the formula:



The term "mono- or disubstituted alkyl- and/or alkylcarbonyl-amino group", represents amino groups substituted by one or two substituents selected from the same or different said lower alkyl or lower alkylcarbonyl group is intended to mean a C₁-C₁₀ alkyl- and/or alkylcarbonyl-amino group, such as, methylamino, ethylamino, propylamino, butylamino, cyclohexylamino, dimethylamino, diethylamino, N-methylbutylamino, acetylamino, propanoylamino, pivaloylamino, N-methylacetylamino and N-ethylacetylamino group, etc..

The term "halogen atom" is intended to mean a fluorine atom, a chlorine atom, a bromine atom and an iodine atom.

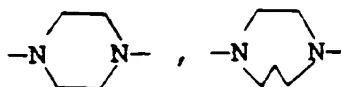
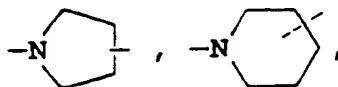
According to the above-described definitions, the R¹ in the general formula [I] includes a hydrogen atom, or an unsubstituted or substituted alkyl group, alkenyl group, aralkyl group and alkylacyl group.

Suitable specific examples of the alkyl group include methyl, ethyl, propyl, isopropyl, butyl, cyclopropyl, cyclopropylmethyl, trifluoromethyl, methoxymethyl, methoxyethoxymethyl, aminoethyl, and the like. Suitable specific examples of the alkenyl group include allyl, 2-methylallyl, 2-butenyl, 3-methyl-2-butenyl, 2-fluoroallyl, 3-fluoroallyl, 2-(trifluoromethyl)allyl, 3-butenyl, and the like. Suitable specific examples of the aralkyl group include benzyl, 4-fluorobenzyl, 4-chlorobenzyl, 3-(trifluoromethyl)benzyl, 4-methoxybenzyl, 2-phenylethyl, 2-[(2-trifluoromethyl)phenyl]ethyl, triphenylmethyl, (4-methoxyphenyl)diphenylmethyl, 2-thienylmethyl, and the like. Suitable specific examples of the alkylacyl group include acetyl, trifluoroacetyl, propanoyl, 2-methylpropanoyl, butanoyl, and the like.

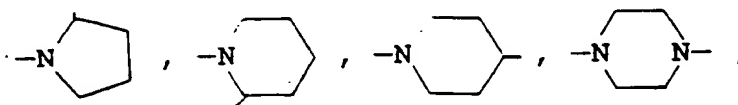
The R² and R³ in the general formula [I] are respectively identical with the R¹, and suitable examples thereof as well are identical with those of R¹. The R² and R³ may be taken together with an adjacent nitrogen atom to form a cyclic amino group. The cyclic amino group is a saturated five- to seven-membered ring and may further have at least one cyclic hetero atom (for example, N, O or S) in its ring other than the above-described nitrogen. Suitable specific examples of the cyclic amino group include 1-pyrrolidinyl, piperidino, 1-piperazinyl, 4-[bis(4-fluorophenyl)methyl]-1-piperazinyl, morpholino, thiomorpholino, 1-perhydro-[1,4]diazepinyl, and the like.

The R^4 and R^5 in the general formula [I] each independently represent a hydrogen atom, a halogen atom or an substituted or substituted alkyl group. Suitable specific examples of the halogen atom include a fluorine atom, a chlorine atom and a bromine atom. Suitable examples of the alkyl group include methyl, ethyl and trifluoromethyl.

In the general formula [I], the Y represents a linking group, which is bonded to the pyrimidine ring via a nitrogen atom therein. of the formula



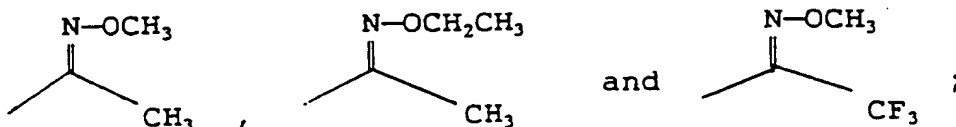
or $-N(G)-$, wherein G represents a hydrogen atom or an alkyl group. Suitable specific examples of the same include groups of the formula:



$-NH-$, $-N(CH_3)-$ and $-N(C_2H_5)-$.

In the general formula [I], where Z bonds with a carbon atom or nitrogen atom in the linking group, suitable specific examples thereof include a hydrogen atom; an alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, cyclohexyl, dimethylaminoethyl, morpholinoethyl, piperidinoethyl, and the like; an alkenyl group such as allyl, 2-methylallyl, 2-butenyl, 3-methyl-2-butenyl, 2-fluoroallyl, 3-fluoroallyl, 2-(trifluoromethyl)allyl, 3-butenyl, and the like; an aralkyl group such as benzyl, 4-fluorobenzyl, 4-chlorobenzyl, 3-(trifluoromethyl)benzyl, 4-methoxybenzyl, 1-phenylethyl, 1-methyl-1-phenylethyl, 2-phenylethyl, 2-(4-fluorophenyl)ethyl, 2-(4-chlorophenyl)ethyl, 2-(4-methoxyphenyl)ethyl, 2-[2-(trifluoromethyl)phenyl]ethyl, cinnamyl, diphenylmethyl, bis(4-fluorophenyl)methyl, 1-(1-naphthyl)ethyl, 1,2,3,4-tetrahydronaphthalene-1-yl, 2-pyrrolyl-methyl, 2-furfuryl, 2-thienylmethyl, and the like; an alkylcarbonyl group such as acetyl, trifluoroacetyl, propanoyl, 2-methylpropanoyl, butanoyl, pivaloyl, cyclopropylcarbonyl, and the like; an arylcarbonyl group such as benzoyl, 4-fluorobenzoyl, 4-chlorobenzoyl, 3-methoxybenzoyl, 4-toluoyl, 1-naphthoyl, 1-pyrrolocarbonyl, 2-furylcarbonyl, 2-thiophenecarbonyl, and the like; and an aralkylcarbonyl group such as phenylacetyl, 4-fluorophenylacetyl, 3-phenylpropanoyl, cinnamoyl, diphenylacetyl, and the like.

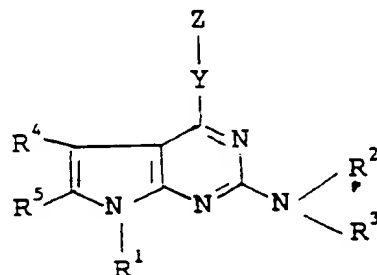
Where Z bonds with a carbon atom in the linking group, suitable other specific examples include a carboxyl group; hydroxyl group; alkoxy carbonyl group such as methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl and tert-butyloxycarbonyl; alkylcarbonyloxy group such as acetyloxy, propanoyloxy, 2-methylpropanoyloxy and pivaloyloxy; arylcarbonyloxy group such as benzoyloxy, 4-fluorobenzoyloxy, 4-toluoyloxy, 4-chlorobenzoyloxy, 4-methoxybenzoyloxy and 1-naphthoyloxy; aralkylcarbonyloxy group such as phenylacetoxyl, 4-fluorophenylacetoxyl, 3-phenylpropanoyloxy, 4-phenylbutanoyloxy and cinnamoyloxy; alkoxy group such as methoxy, ethoxy, propoxy, isopropoxy and butoxy; and an alkoxyiminoalkyl group such as groups of the formula:




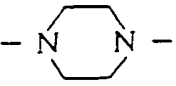

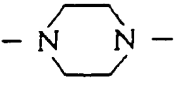


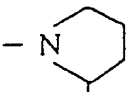

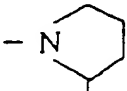
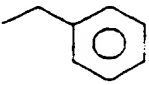

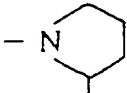

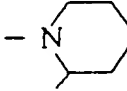

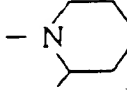

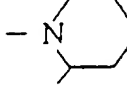
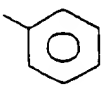

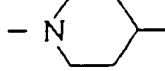
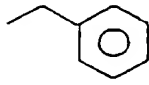

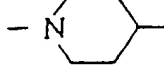
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
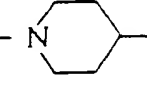

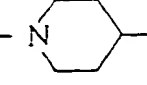
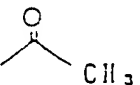

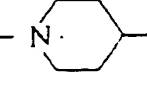
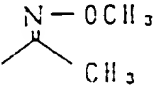

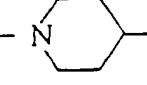

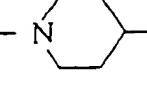

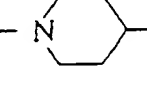

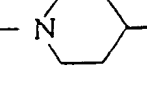

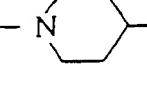

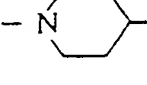
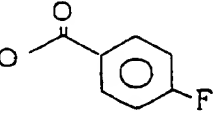

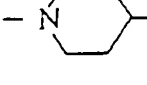

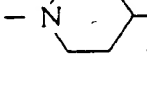
Further, preferably Y and Z taken together represent a morpholino group and thiomorpholino group.


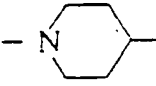


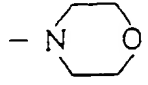

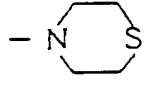

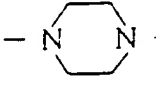

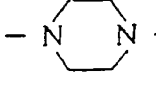

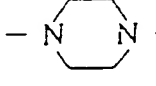

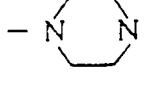
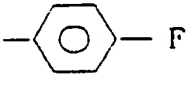

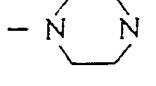
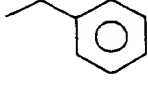

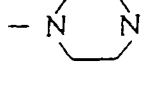
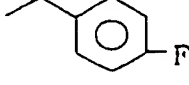

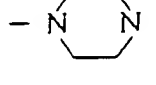
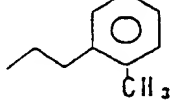

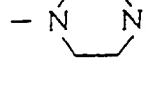
Suitable specific examples of pyrrolo[2,3-d]pyrimidine of the general formula [I] in accordance with the present invention include the compounds containing the substituents described in the following table. Note, when the compound has asymmetric carbon atoms in structure thereof, the compounds of the present invention include all optical isomers.









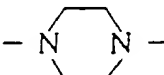


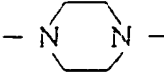
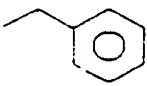
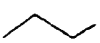

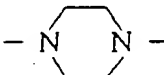


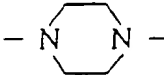
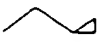

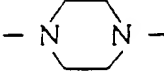


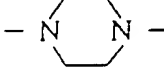
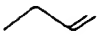

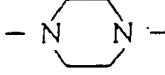
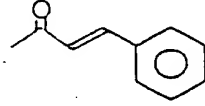
Table

... [I]

	Compound No.	R ¹	R ²	R ³	R ⁴	R ⁵	Y	Z
5	101	H	H		H	H		F ₂ BH ¹¹
10	102	H	H		CH ₃	CH ₃		F ₂ BH ¹¹
15	103	CH ₃	H	CH ₃	H	H		F ₂ BH ¹¹
20	104	CH ₃	H		H	H		H
25	105	CH ₃	H		H	H		
30	106	CH ₃	H		H	H		CO ₂ H
35	107	CH ₃	H		H	H		H
40	108	CH ₃	H		Cl	H		H
45	109	CH ₃	H		H	H		
50	110	CH ₃	H		H	H		
55	111	CH ₃	H		H	H		F ₂ BH ¹¹

	Compound No.	R ¹	R ²	R ³	R ⁴	R ⁵	Y	Z
5	112	CH ₃	H		CH ₃	H		F ₂ BH ¹¹
10	113	CH ₃	H		H	H		
15	114	CH ₃	H		H	H		
20	115	CH ₃	H		H	H		CO ₂ H
25	116	CH ₃	H		H	H		CO ₂ -iPr
30	117	CH ₃	H		H	H		OH
35	118	CH ₃	H		H	H		OCH ₂ CH ₃
40	119	CH ₃	H		H	H		OAc
45	120	CH ₃	H		H	H		
50	121	CH ₃	H		H	H		NHCH ₂ CH ₃
55	122	CH ₃	H		H	H		NH-Ac

	Compound No.	R ¹	R ²	R ³	R ⁴	R ⁵	Y	Z
5	123	CH ₃	H		H	H		N 
10	124	CH ₃	H		H	H		
15	125	CH ₃	H		H	H		
20	126	CH ₃	H		H	H		CH ₃
25	127	CH ₃	H		CH ₃	CH ₃		CH ₃
30	128	CH ₃	H		H	H		CH ₂ CH ₃
35	129	CH ₃	H		H	H		
40	130	CH ₃	H		H	H		
45	131	CH ₃	H		H	H		
50	132	CH ₃	H		H	H		
55	133	CH ₃	H		H	H		F ₂ BH ¹¹

	Compound No.	R ¹	R ²	R ³	R ⁴	R ⁵	Y	Z
5	134	CH ₃	H		H	H		F ₂ BH ¹⁾
10	135	CH ₃	H		H	H		2)
15	136	CH ₃	CH ₃		H	H		F ₂ BH ¹⁾
20	137	CH ₃			H	H		F ₂ BH ¹⁾
25	138	CH ₃	Ac		H	H		OAc
30	139	CH ₃	H	MMTr ³⁾	H	H		
35	140		H		H	H		F ₂ BH ¹⁾
40	141		H		H	H		F ₂ BH ¹⁾
45	142		H		H	H		F ₂ BH ¹⁾
50	143		H		H	H		F ₂ BH ¹⁾
55	144		H		H	H		

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


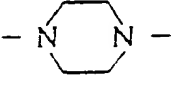
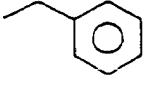

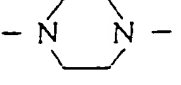
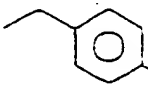
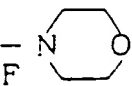
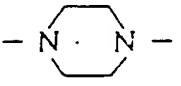
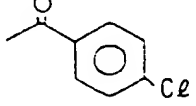

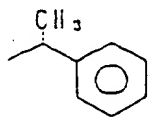


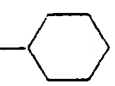



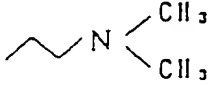
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
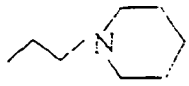

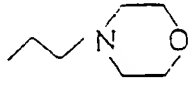

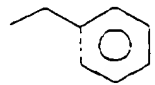

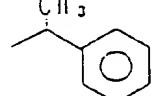

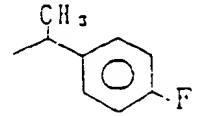

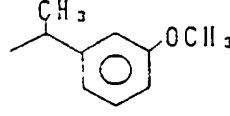

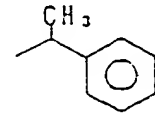

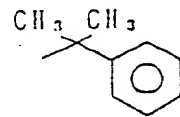

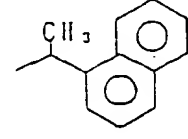

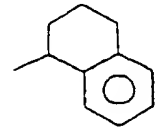
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Compound No.	R ¹	R ²	R ³	R ⁴	R ⁵	Y	Z
145				H	H		F ₂ BH ¹¹
146		H		H	H		F ₂ BH ¹¹
147				H	H		
148	CH ₃	H		H	H	-NH-	
149	CH ₃	H		H	H	-NH-	H
150	CH ₃	H		H	H	-NH-	
151	CH ₃	H		H	H	-NH-	
152	CH ₃	H		H	H	-NH-	

	Compound No.	R ¹	R ²	R ³	R ⁴	R ⁵	Y (G)	Z
5	153	CH ₃	H		H	H	-NH-	
10	154	CH ₃	H		H	H	-NH-	
15	155	CH ₃	H		H	H	-NH-	
	156	CH ₃	H		H	H	-NH-	
20	157	CH ₃	H		H	H	-NH-	
25	158	CH ₃	H		H	H	-NH-	
30	159	CH ₃	H		CH ₃	CH ₃	-NH-	
35	160	CH ₃	H		H	H	-NH-	
40	161	CH ₃	H		H	H	-NH-	
45	162	CH ₃	H		H	H	-NH-	

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
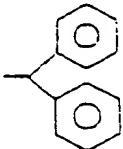

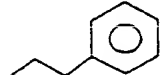


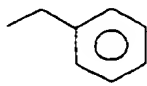

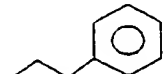

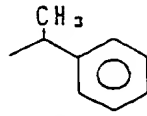

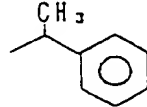
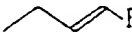
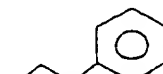



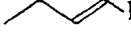
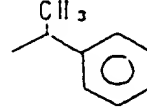
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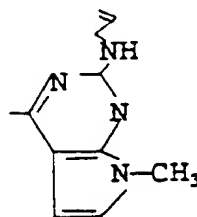
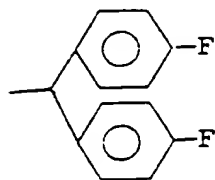
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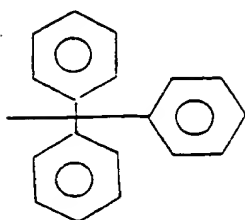
Compound No.	R ¹	R ²	R ³	R ⁴	R ⁵	Y (G)	Z
163	CH ₃	H		H	H	-NH-	
164	CH ₃	H		H	H	-NH-	
165	CH ₃	H		H	H	-N(CH ₃)-	CH ₃
166	CH ₃	H		H	H	-N(CH ₃)-	
167	CH ₃	H		H	H	-N(CH ₃)-	
168	CH ₃	H		H	H	-N(CH ₂ CH ₃)-	
169	CH ₃	H	 CH ₃	H	H	-NH-	
170	CH ₃	H		H	H	-NH-	
171		H		H	H	-N(CH ₃)-	CH ₃
172		H		H	H	-NH-	

wherein

$F_2BH^{1)}$, $^{2)}$ and $MMTr^{3)}$ represent



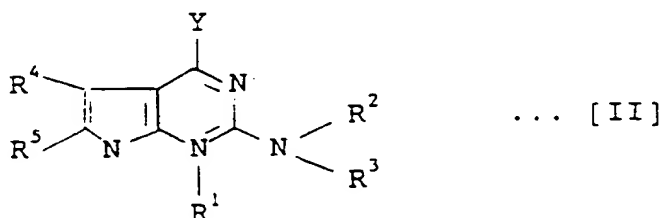
and



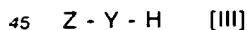
OCH_3 , respectively.

The pyrrolo[2,3-d]pyrimidine derivatives in accordance with the present invention may be acid addition salts, and suitable examples of acids forming such salts include inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, boric acid, carbonic acid, and the like; organic carboxylic acids such as formic acid, acetic acid, propionic acid, citric acid, succinic acid, maleic acid, oxalic acid, tartaric acid, maleic acid, fumaric acid, and the like; and organic acids such as methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluene-sulfonic acid, camphorsulfonic acid, and the like.

According to the present invention, a pyrrolo[2,3-d]pyrimidine derivative and pharmaceutically acceptable acid addition salt thereof can be produced by reacting a halogenated pyrrolo[2,3-d]pyrimidine derivative, or acid addition salt, represented by the general formula [II]



wherein R^1 , R^2 , R^3 , R^4 and R^5 have the meanings defined in the formula [I] of claim 1, and X represents a halogen atom with an amine compound represented by the general formula [III]



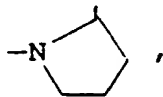
wherein Y and Z have the same meanings as defined in the above formula [I], followed by mixing with an inorganic or organic acid, if necessary.

The halogenated pyrrolo[2,3-d]pyrimidine derivative represented by the formula [II] [wherein R^1 to R^5 have the meanings defined above in connection with the R^1 to R^5 in the formula [I] and X represents a halogen atom] may be a novel or known compound. With respect to the known compound, a process for producing same is also known in the art [see, for example, F. Seela et al., *Liebigs Ann. Chem.*, 137 (1983); and M. Legraverend et al., *Tetrahedron Lett.*, Vol. 26, 2001 (1985)].

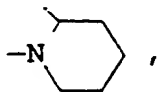
Also a novel compound can be prepared according to a process of producing a similar known compound. Examples of the halogen atom in the halogenated pyrrolo[2,3-d]pyrimidine derivative include a chlorine atom, a bromine atom and an iodine atom. Such atoms are highly reactive, and a pyrrolo[2,3-d]pyrimidine derivative of interest, represented by the formula [I], can be produced by reacting such atoms with a amine compound represented by the formula [III] wherein Y and Z have the meanings defined above

in connection with the Y and Z in the formula [I].

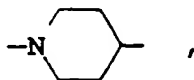
The amine compound represented by the formula [III], as such, is known in the art, or may be produced according to a known process. Suitable specific examples of the above-described amine compound when Y represents a linking group of the formula:



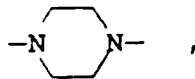
include pyrrolidine, 2-methylpyrrolidine, 2-hydroxymethylpyrrolidine, 2-benzylpyrrolidine, 2-phenylpyrrolidine, 2-carboxypyrrolidine and 2-methoxycarbonylpyrrolidine; when Y represents a linking group of the formula:



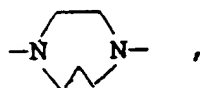
include piperidine, 2-methylpiperidine, 2-hydroxymethylpiperidine, 2-benzylpiperidine, 2-phenylpiperidine, 2-carboxypiperidine and 2-methoxycarbonylpiperidine; when Y represents a linking group of the formula:



include 4-hydroxypiperidine, 4-methylpiperidine, 4-ethylpiperidine, 4-benzylpiperidine, 4-(4-fluorobenzyl)piperidine, 4-[bis(4-fluorophenyl)methyl]piperidine, 4-phenylpiperidine, 4-acetyloxypiperidine, 4-propanoyloxypiperidine, 4-benzoyloxypiperidine, 4-(4-fluorobenzoyloxy)piperidine, 4-(4-chlorobenzoyloxy)piperidine, 4-(phenylacetyloxy)piperidine, 4-acetyl piperidine, 4-propanoylpiperidine, benzoylpiperidine, 4-(1-methoxyimino)ethylpiperidine, 4-carboxypiperidine, 4-isopropylloxycarbonylpiperidine, 4-methoxypiperidine, 4-ethoxypiperidine, 4-(methylamino)piperidine, 4-(N,N-dimethylamino)piperidine, 4-(acetylamino)piperidine and 4-(N-methyl-N-acetylamino)piperidine; when Y represents a linking group of the formula:



include N-methylpiperazine, N-(2-methoxyethyl)piperazine, N-allylpiperazine, N-phenylpiperazine, N-benzylpiperazine, N-(4-fluorophenyl)piperazine, N-(4-fluorobenzyl)piperazine, N-(2-phenylethyl)piperazine, N-[2-(2-(trifluoromethyl)phenyl)ethyl]piperazine, N-cinnamylpiperazine, N-[bis(4-fluorophenyl)methyl]piperazine, N-acetyl piperazine, N-(4-fluorobenzoyl)piperazine, N-(4-chlorobenzoyl)piperazine, N-(4-fluorophenylacetyl)piperazine and N-cinnamoylpiperazine; and when Y represents a linking group of the formula:



include N-methylperhydro[1,4]diazepine, N-allyl-perhydro[1,4]diazepine, N-benzyl-perhydro[1,4]diazepine, N-(2-phenylethyl) perhydro[1,4]diazepine, N-[bis(4-fluorophenyl)methyl]perhydro[1,4]diazepine and N-acetylperhydro[1,4]diazepine; when Y represents a linking group of the formula: -NH-, include ammonia, allylamine, 2-methylallylamine, methylamine, cyclohexylamine, benzylamine, 4-fluorobenzylamine, 4-chlorobenzylamine, 4-methoxybenzylamine, 1-phenylethylamine, 1-methyl-1-phenylethylamine, 2-phenylethylamine, 2-(4-fluorophenyl)ethylamine, 2-(4-chlorophenyl)ethylamine, 2-(4-methoxyphenyl)ethylamine, 1,1-diphenylmethylamine, 1,1-bis(4-fluorophenyl)methylamine, cinnamylamine, 1-(1-naphthyl)ethylamine, 1,2,3,4-tetrahydronaphthalene-1-yl amine, 2-(N,N-dimethylamino)ethylamine, 2-mor-

pholinoethylamine and 2-piperidinoethylamine; when Y represents a linking group of the formula: $-N(CH_3)-$ or $-N(C_2H_5)-$, include dimethylamine, diethylamine, N-methylbenzylamine, N-methyl(2-phenylethyl)amine, N-ethylbenzylamine, N-methyl(1-phenylethyl)amine and N-ethyl-(1-phenylethyl)amine; when Y and Z taken together represent a group -Y-Z, include morpholine and thiomorpholine.

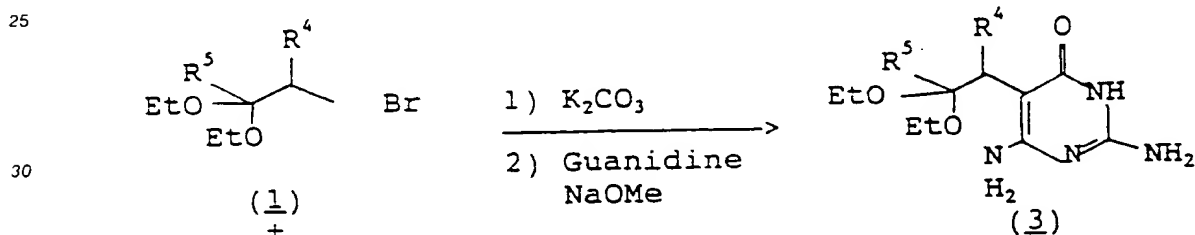
5 The above-described reaction can be conducted, for example, by reacting one equivalent of a halogenated pyrrolo[2,3-d]pyridine derivative represented by the formula [II] with 1 to 30 equivalents of an amine compound represented by the formula [III] in the absence or presence of a solvent. If necessary, a base also may be present in the reaction system, and examples of the base include inorganic bases such as sodium hydroxide, potassium hydroxide, sodium carbonate and potassium carbonate, and organic bases
10 such as triethylamine, diethylaniline, dimethylaniline and pyridine.

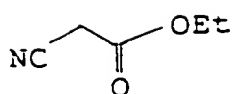
The reaction temperature is from -20 to 300°C , preferably from a room temperature to 200°C , and the reaction time is usually 72 hours or less.

Examples of the reaction solvent include halogenated hydrocarbons such as dichloromethane, chloroform, trichloroethane and carbon tetrachloride; aromatic hydrocarbons such as benzene, toluene and
15 xylene; alcohols such as methanol, ethanol, isopropyl alcohol, butanol and tert-butanol; ethers such as diethyl ether, tetrahydrofuran and dioxane; and aprotic polar solvents such as dimethylformamide, dimethylacetamide, dimethylsulfoxide and sulfolane.

After the completion of the reaction, the desired product, a pyrrolo[2,3-d]pyrimidine derivative represented by the formula [1], can be isolated by general separating and purifying procedure, i.e., concentration,
20 extraction, recrystallization, and chromatography, etc. The compound [I] can be also converted to a pharmaceutically acceptable acid addition salt according to a conventional method.

The entire steps of the reaction, including general steps utilized for producing the above-described starting material of the formula [II], are as follows:

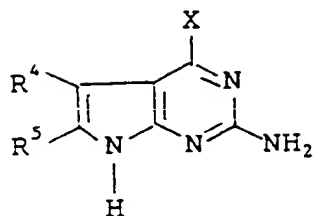




(2)

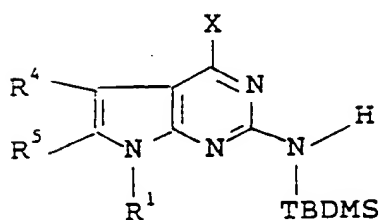
1) HCl

2) Halogenation



(4)

1) TBDMSOTf

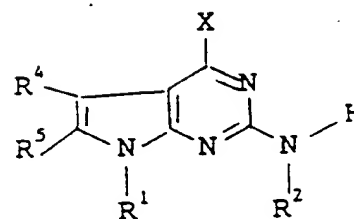
2) K₂CO₃R¹X

(5)

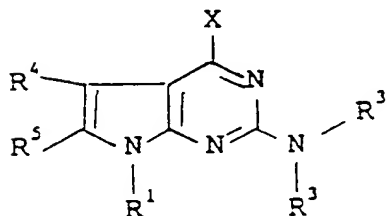
1) NaH

R²X

2) HCl

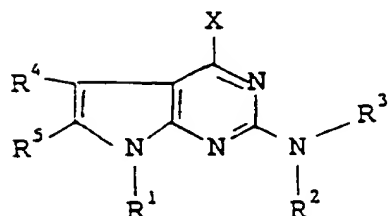


(6)



[II]

Z - Y - H [III]



wherein R¹, R², R³, R⁴ and R⁵, as well as X, Y and Z, have the meanings as defined above, and TBDMSOTf represents tert-butyl-dimethyl-silyl-trifluoromethanesulfonate.

The reaction steps for the compound of formula [II] are summarized as follows:

The compound of the formula (3) can be obtained by a reaction of acetal (1) with ethyl cyanoacetate (2) in an alkaline condition, following by a ring-closing reaction using guanidine in the presence of a strong base.

The compound of formula (4) can be obtained by a ring-closing reaction of the resulting compound (3) in the presence of hydrochloric acid, followed by a halogenation according to a usual method, e.g., with phosphorus oxychloride.

The compound of formula (5) can be obtained by a silylation of the resulting compound (4) with TBDMSOTf, followed by a reaction with R^1X , wherein X is a halogen atom, in an alkaline condition.

The compound of formula (6) can be obtained by a reaction of the resulting compound (5) with R^5X in the presence of a strong base, followed by a desilylation with hydrochloric acid.

The compounds, to which are selectively introduced the substituents R^1 , R^2 and R^3 , of the formula [II] can be obtained by a reaction of the final compound (6) with R^3X , in the presence of a strong base.

The present compounds exhibit an excellent pharmacological action against hypoxemia associated with various respiratory diseases. It is generally known that, in pneumonopathy, e.g., pneumonectasis, bronchitis, bronchial asthma, interstitial pneumonia and pneumonophthisis, the partial pressure of oxygen (PaO_2) in arterial blood lowers according as the pathosis is severer or chronic. In this case, symptoms such as a feeling of fatigue, shortness of breath and choking feeling occur, and in a serious state, dyspnea, cyanosis and a disturbance of consciousness occur.

Therefore, a pharmaceutical preparation capable of raising and improving the PaO_2 lowered due to such respiratory diseases has been desired in the art. Further, it is often shown that, in such diseases, the partial pressure of carbon dioxide ($PaCO_2$) in arterial blood increases conversely to a decrease of PaO_2 , and in this case, there is a need for a pharmaceutical preparation that can not only increase $PaCO_2$ but also decrease PaO_2 .

The compounds in accordance with the present invention have actions such that they enhance the respiratory function of the lung, that one mainly increases only PaO_2 , and that another increases PaO_2 and decreases $PaCO_2$, at the same time, and thus the present compounds are useful for the treatment of hypoxemia associated with various respiratory diseases.

The pharmacological effect of the compound in accordance with the present invention can be demonstrated by an acute hypoxemia model using an experimental animal. For example, the acute hypoxemia (having a lower PaO_2 value) model can be prepared by administering intratracheally a fine powder, such as carbon powder, silica gel, glass beads or dental impression material, in a small animal, e.g., rat, to lower the respiratory function [see, for example, Munakata et al., Preprints of the 35th Symposium of Japan Society of Anesthesiology, 179 (1988)]. Also the acute hypoxemia (having a lower PaO_2 value) model can be prepared by administering intratracheally a mucosa-prophlogistic acid, e.g., acetic acid and crotonic acid. Therefore, the compounds in accordance with the present invention were orally or, parenterally administered to the above-described model animal, and the arterial blood was collected after a given period of time and subjected to a measurement of PaO_2 (or $PaCO_2$) by a blood gas analyzer. As a result, a significant increase of PaO_2 (or decrease of $PaCO_2$) in comparison with that before the administration, was observed.

The pyrrolo[2,3-d]pyrimidine derivative and its acid addition salt in accordance with the present invention can be administered orally or as a parenteral administration such as an intravenous, subcutaneous, intramuscular, percutaneous, intrarectal or other administration.

Examples of the dosage form for the oral administration include tablets, pills, granules, powders, suspensions and capsules.

The tablets can be formulated by a conventional method through the use of, for example, excipients such as lactose, starch and crystalline cellulose; binders such as carboxymethylcellulose, methylcellulose and polyvinylpyrrolidone; and disintegrators such as sodium alginate, sodium hydrogencarbonate and sodium laurylsulfate.

Similarly, the pills, powders and granules can be formulated by a conventional method through the use of the above-described excipients, etc. The solutions and suspensions can be formulated by a conventional method through the use of, for example, glycerin esters such as tricaprylin and triacetin and alcohols such as ethanol. The capsules can be formulated by filling a granule, a powder or a solution into a capsule made of gelatin, and the like.

Examples of the dosage form for a subcutaneous, intramuscular and intravenous administration include injections in the form of an aqueous or nonaqueous solution. In the aqueous solution, use is made of, for example, a physiological saline, and the like. In the nonaqueous solution, use is made of, for example, propylene glycol, polyethylene glycol, olive oil, ethyl oleate, and the like. If necessary, preservatives, stabilizers, etc., may be added thereto. The injections can be sterilized by a proper treatment, such as a filtration through the bacterial filter, or by an addition of a bactericide.

Examples of the dosage forms for a percutaneous administration include ointments and creams. The ointments and creams can be formulated by a conventional method through the use of fatty oils, such as

castor oil and olive oil, petrolatums, etc., in the case of the ointments, and emulsifiers, such as diethylene glycol and sorbitan monofatty acid esters, etc., in the case of the creams.

Conventional suppositories, such as gelatin soft capsules, may be used for a rectal administration.

Although the dosage of the pyrrolo[2,3-d]pyrimidine derivative of the present invention varies depending upon the kind of disease, administration path, age and sex of patient, and severity of disease, etc., it is usually 1 to 500 mg/day/adult.

All of the compounds provided by the present invention (testing substances) have more than 2 g/kg (rat, P.O.) of LD₅₀.

10 EXAMPLES

The present invention will now be described in more detail with reference to the following Examples.

Reference Example: Synthesis of 2-allylamino-4-chloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidine

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Procedure A:

A mixture of 5.00 g (29.6 mmol) of 2-amino-4-chloro-7H-pyrrolo[2,3-d]pyrimidine, 10.08 g (1.1 eq.) of p-anisylchlorodiphenylmethane, and 4.96 ml (12 eq.) of triethylamine in 65 ml of dimethylformamide (DMF) was stirred at room temperature for 30 min. After cooling to 0°C, 4.50 ml (2.44 eq.) of methyl iodide and 3.00 g (2.53 eq.) of sodium hydride were added in order, and the mixture was stirred for one hour. And then, 5.36 ml (1.5 eq.) of allyl iodide and 2.00 (2.5 eq.) of sodium hydride were added to the reaction mixture followed by additional one hour stirring at 0°C. Finally 200 ml of 2N hydrochloric acid and 100 ml of diethyl ether were added and stirred for one hour at room temperature. The reaction mixture was neutralized with sodium bicarbonate and extracted with three portion of 100 ml of ethylacetate. The combined organic layer was washed with brine, dried over anhydrous magnesium sulfate. The solvents were removed in vacuo. The residual oily mixture was purified with silica-gel column chromatography (hexane: ethylacetate = 8:1 as elutant), to give 3.51 g (53.1 %) of 2-allylamino-4-chloro-7-methyl-7H-pyrrodo[2,3-d]pyrimidine.

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Procedure B:

To 300 ml of methylene chloride was added 26.9 g (159.5 mmol) of 2-amino-4-chloro-7H-pyrrolo[2,3-d]pyrimidine and 111 ml (5 eq.) of triethylamine, and the mixture was stirred at -30°C. Then 36.7 ml (1.1 eq.) of tert-butyldimethylsilyl trifluoromethane sulfonate was slowly dropwised to the mixture, and reacted for 1.5 hours. The crystals were completely dissolved to form a light brown solution. The mixture was allowed to warm to room temperature and filtrated with 200 g of silica-gel on a glass-filter. The filtrate and an elute eluted with 1 l of methylene chloride was combined. After evaporation of the solution, to the oily residue was added 300 ml of aqueous 1N NaOH, and the aqueous solution was extracted with hexane (500 ml x 4). The combined organic layer was washed with water and brine in order, dried over anhydrous magnesium sulfate, and removed the solvents in vacuo. The resulting crystals were recrystallized from hexane, to give 35.27 g (yield 78.2%) of 2-tert-butyl-dimethylsilylamino-4-chloro-7H-pyrrolo[2,3-d]pyrimidine in the form of light brown plates (m.p. 114°C)

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Physical Property:

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¹H-NMR (CDCl₃) δ:

0.30(s, 6H), 0.98(s, 9H), 4.5(br-s, 1H)

6.4H(m, 1H) 6.9(m, 1H), 8.3(br-s, 1H)

Then, 44.0 g (115.6 mmol) of tert-butyldimethyl silylamino-4-chloro-7H-pyrrolo[2,3-d]pyrimidine and 13.5 ml (1.4 eq.) of methyl iodide in 150 ml of DMF, and 34.40 g (1.6 eq.) of potassium carbonate was reacted at room temperature for 15 hours with vigorous stirring. After addition of water to the reaction mixture, the aqueous solution was extracted with hexane (200 ml x 4), washed with brine, and dried over anhydrous magnesium sulfate. The solvents were removed in vacuo, to give 45.87 g (154.5 mmol) (quantitative yield) of 2-ter-butyldimethylsilylamino-4-chloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidine in the form of light yellow crystals. Under nitrogen atmosphere the crystals and 21.19 ml (1.5 eq.) of allyl iodide wer dissolved in 300 ml of DMF, and the reaction mixture was cooled to 0°C with vigorous stirring, then 9.27 g (1.5 eq.) of sodium hydride (60%), thoroughly washed by hexane, was added to that as hexane suspension.

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The mixture was stirred for 10 min., and then 300 ml of water was slowly added to stop the reaction. The aqueous solution was extracted with hexane (300 ml x 4), the combined organic layer was washed with

water and brine, and dried over anhydrous magnesium sulfate. After evaporation, 53.5 g of a yellow oily residue was given. The residue was dissolved in 30 ml of diethylether, and to the solution 50 ml of concentrated hydrochloric acid was added at 0°C with stirring, and the mixture was reacted for 10 min. After the reaction was completed, to the solution was added diethylether (100 ml x 2) to separate the organic layer. The aqueous layer was diluted with 200 ml of ice-water, and then neutralized with a 5N NaOH aqueous solution.

The Resulting precipitate was extracted with ethylacetate (250 ml x 3), the extract was washed with water and brine, dried over anhydrous magnesium sulfate, and evaporated, to give 33.57 g (yield 97.6%) of 2-allylamino-4-chloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidine in the form of light yellow crystals.

The crystals were recrystallized from ethylalcohol to give 32.57 g (yield 94.0%) of the above-described compound as yellowish white plates (m.p. 113-114°C)

Physical Properties:

¹H-NMR (CDCl₃), δ:

3.67(s, 3 H), 4.0-4.2(m, 2H), 3.9-5.4(m, 3H), 5.75-6.25(m, 1H), 6.34(d, 1H, J = 3.5 Hz), 6.77(d, 1H, J = 3.5 Hz).

Elemental analysis: for C ₁₀ H ₁₁ N ₄ Cl,			
Calculated:	C, 53.94;	H, 4.98;	N, 25.16
Found:	C, 53.90;	H, 4.98;	N, 25.11

Example 1: Synthesis of (±)-2-allylamino-7-methyl-4-(1-phenylethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine and its hydrochloride (156)

To 70 ml of n-butylalcohol was added 32.5 g (146.0 mmol) of 2-allylamino-4-chloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidine prepared in Reference Example, 26.22 g (1.3 eq.) of potassium carbonate and 88 g (5.0 eq.) of (±)-phenyl-ethylamine, the mixture was stirred in an autoclave equipped with a stirrer at 165°C (5 atm) for 5 hours. After cooling to room temperature, 400 ml of water was added, and the mixture was extracted with ethylacetate (250 ml x 3). Combined organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and then the solvents and unreacted (±)-phenylethyl-amine were removed in vacuo. The red oily residue was crystallized with isopropylalcohol, to give 40.38 g (yield 90.0%) of (±)-2-allylamino-7-methyl-4-(1-phenylethyl-amino)-7H-pyrrolo[2,3-d]pyrimidine [(156) free base] in the form of crude crystals. They were recrystallized from isopropylalcohol to give 37.56 g (yield 83.7%) of colorless needles (m.p. 112-112.5°C). Then 30.00 g of the free base was dissolved in 800 ml of diethylether, and a saturated hydrochloric acid ethereal solution was added to form hydrochloride.

The diethylether and excess hydrochloric acid were evaporated and the resulting oily residue was crystallized with acetone.

The crystals were washed with acetone, and dried in vacuo at 80°C, to give 33.08 g (yield from the free base, 98.6%) of (±)-2-allylamino-7-methyl-4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidine hydrochloride [(156) HCl · salt] in the form of colorless crystals (m.p. 167-170°C).

Physical Properties

The Free Base

¹H-NMR (CDCl₃) δ:

1.60 (d, 3H, J = 6.8), 3.60(s, 3H), 4.0(t, 2H, J = 5.7), 4.65(br-t, 1H, J = 5.7), 4.95(br-s, 1H), 4.9-5.4(m, 2H), 5.43(t, 1H, J = 6.8), 5.7-6.2(m, 1H), 6.11(d, 1H, J = 3.5), 6.54(d, 1H, J = 3.5), 7.2-7.5(m, 5H)

IR(KBr) ν max, cm⁻¹

3240, 1620, 1560, 1450, 1285

UV(EtOH) λ max, nm

295, 228

Elemental analysis: for C ₁₅ H ₂₁ N ₅ ,			
Calculated:	C, 70.33;	H, 6.89;	N, 22.78.
Found:	C, 70.38;	H, 7.01;	N, 22.63.

The HydrochlorideIR(KBr) ν max, cm^{-1}

3240, 1620, 1560, 1450, 1285

5 UV(EtOH) λ max, nm

296, 236, 207

Elemental analysis: for $\text{C}_{19}\text{H}_{22}\text{N}_5\text{Cl}$.				
Calculated:	C, 62.87;	H, 6.45;	N, 20.37;	Cl, 10.26
Found:	C, 62.84;	H, 6.40;	N, 20.23;	Cl, 10.29.

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15 In the following Examples, the compounds of the present invention were prepared by the procedures described in Example 1, using corresponding starting materials and reactants, respectively, as well as reaction solvents and coexisting bases indicated in the following tables, and each reaction was performed under the condition, i.e., reaction temperature, reaction times, and reaction vessel, indicated in said tables.

(*A: Autoclave B: Normal pressure and open system)

Ex. No.	Com- pound No.	¹ H-NMR data of free base. (CDCl ₃) δ (ppm)	Yield of free base (%)	Type of salt M.P. of acid addition unit Recrystallization solvent	UV of acid addition unit EtOH (nm)	Reaction solvent Coexisting base	Reaction temp. Reaction time Reaction vessel
2	101	2.47 (t-like, 4H, J=5Hz), 3.7-4.1 (m, 6), 4.25 (s, 1H), 4.9-5.3 (m, 3H), 5.7-6.1 (m, 1H), 6.28 (d, 1H, J=3.7Hz), 6.70 (d, 1H, J=3.7Hz), 6.8-7.5 (m, 9H)	71	HCℓ · salt 180-184 °C (dec.) i-PrOH	299 233 207	n-BuOH K ₂ CO ₃	120 °C 14h B
3	103	2.46 (t-like, 4H, J=5Hz), 2.9-3.0 (m, 3H), 3.61 (s, 3H), 3.88 (t-like, 4H, J=5Hz), 4.23 (s, 1H), 4.3-4.7 (m, 1H), 6.23 (d, 1H, J=3.6Hz), 6.56 (d, 1H, J=3.6), 6.8-7.5 (m, 8H)	74	HCℓ · salt	—	n-BuOH K ₂ CO ₃	120 °C 5h B
4	104	1.9-2.1 (m, 4H), 3.62 (s, 3H), 3.6-3.9 (m, 4H), 4.0-4.2 (m, 2H), 4.6 (br-s, 1H), 5.0-5.4 (m, 2H), 5.8-6.3 (m, 1H), 6.35 (d, 1H, J=3.5Hz), 6.54 (d, 1H, J=3.5Hz)	74	HCℓ · salt 193-195 °C i-PrOH	302 267 237	n-BuOH K ₂ CO ₃	110 °C 8h B
5	105	1.8-2.0 (m, 4H), 2.7 (m, 1H), 3.4 (m, 1H), 3.64 (s, 3H), 3.8 (m, br, 3H), 4.17 (m, 2H), 4.7 (br, 1H), 5.0-5.4 (m, 2H), 5.8-6.3 (m, 1H), 6.38 (d, 1H, J=3.5Hz), 6.57 (d, 1H, J=3.5Hz), 7.25 (s, 5H)	70	HCℓ · salt 150-153 °C i-PrOH	299 237 206	none K ₂ CO ₃	145 °C 20h B
6	106	1.9-2.7 (m, 4H), 3.57 (s, 3H), 3.5-4.4 (m, 5H), 4.8 (br-1H), 4.9-5.4 (m, 2H), 5.7-6.2 (m, 1H), 6.41 (d, 1H, J=3.5Hz), 6.54 (d, 1H, J=3.5Hz), 9.4 (br, 1H)	21	fumarate EtOH	—	n-BuOH K ₂ CO ₃	100 °C 4h B

Ex. No.	Compound No.	¹ H-NMR data of free base (CDCl ₃) δ (ppm)	Yield of free base	Type of salt H.P. of acid addition salt Recrystallization solvent	UV of acid addition salt EtOH λ max (nm)	Reaction solvent Coexisting base	Reaction temp. Reaction time Reaction vessel
7	107	1.5-2.0(m, 6H), 3.61(s, 3H), 3.8-3.95(m, 4H), 4.08(t-like, 2H, J=5.5Hz), 4.6(br, 1H), 4.95-5.4(m, 2H), 5.8-6.3(m, 1H), 6.31(d, 1H, J=3.5Hz), 6.57(d, 1H, J=3.5Hz) 1.6-1.7(br, 4H), 1.8-2.5(br, 2H), 3.1(m, 1H), 3.61(s, 3H), 4.05(m, 2H), 4.6(br, 1H), 4.8(br, 1H), 5.0-5.3(m, 2H), 5.8-6.1(m, 1H), 6.1(br, 1H), 6.16(d, 1H, J=3.5Hz), 6.51(d, 1H, J=3.5Hz), 7.30(s-like, 5H)	100	HCℓ-salt 161-162 °C i-PrOH	—	n-BuOH	110 °C 6h B
8	109	1.1-1.9(m, 5H), 2.54(d, 2H, J=6.6Hz), 2.92(t, 2H, J=11Hz), 3.60(s, 3H), 4.06(t, 2H, J=6Hz), 4.5-4.7(m, 3H), 4.9-5.4(m, 2H), 5.7-6.2(m, 1H), 6.27(d, 1H, J=3.5Hz), 6.56(d, 1H, J=3.5Hz), 7.0-7.4(m, 5H)	45	fumarate 158-159 °C EtOH	233 206	K ₂ CO ₃	150 °C 35h B
9	110	1.1-1.9(m, 5H), 2.54(d, 2H, J=6.6Hz), 2.92(t, 2H, J=11Hz), 3.60(s, 3H), 4.06(t, 2H, J=6Hz), 4.5-4.7(m, 3H), 4.9-5.4(m, 2H), 5.7-6.2(m, 1H), 6.27(d, 1H, J=3.5Hz), 6.56(d, 1H, J=3.5Hz), 7.0-7.4(m, 5H)	100	—	—	n-BuOH K ₂ CO ₃	120 °C 5h B
10	113	1.5-2.1(m, 4H), 2.15(s, 3H), 2.4-2.8(m, 1H), 2.9-3.35(m, 2H), 3.60(s, 3H), 4.07(t, 2H, J=6Hz), 4.5-4.9(m, 3H), 5.0-5.4(m, 2H), 5.7-6.3(m, 1H), 6.28(d, 1H, J=3.5Hz), 6.58(d, 1H, J=3.5Hz)	100	fumarate 164-166 °C EtOH	—	n-BuOH K ₂ CO ₃	120 °C 8h B

Ex. No.	Compound No.	¹ H-NMR data of free base (CDCl ₃) δ (ppm)	Yield of free base	Type of salt H.P. of acid addition salt Recrystallization solvent	UV of acid addition salt EtOH λ max (nm)	Reaction solvent Coexisting base	Reaction temp. Reaction time Reaction vessel
11	114	1.4-2.0(m,7H), 2.2-2.65(m,1H), 2.8-3.2(m,2H), 3.61(s,3H), 3.82(s,3H), 4.07(t,2H, J=6Hz), 4.5-5.4(m,5H), 5.8-6.3(m,1H), 6.29(d,1H, J=3.5Hz), 6.58(d,1H, J=3.5Hz)	30	fumarate 133-134 °C EtOH	—	n-BuOH K ₂ CO ₃	120°C 4h B
12	115	1.3-2.1(m,4H), 2.3-2.7(m,1H), 2.9-4.7(br,1H), 2.95-3.4(m,2H), 3.58(s,3H), 3.8-4.1(m,2H), 4.3-4.8(m,2H), 4.9-5.4(m,2H), 5.6(br-t,1H, J=6Hz), 5.8-6.3(m,1H), 6.29(d,1H, J=3.5Hz), 6.67(d,1H, J=3.5Hz)	98	—	—	n-BuOH K ₂ CO ₃	80 °C 38h B
13	116	1.24(d,6H, J=6.2Hz), 1.5-2.2(m,4H), 2.3-2.7(m,1H), 3.0-3.4(m,2H), 3.69(s,3H), 3.9-4.2(m,2H), 4.3-5.4(m,6H), 5.8-6.4(m,1H), 6.30(d,1H, J=3.7), 6.60(d,1H, J=3.7Hz)	30	fumarate 151-153 °C EtOH	—	n-BuOH K ₂ CO ₃	120°C 4h B
14	117	1.3-2.15(m,4H), 3.38(ddd,2H, J=13Hz, 9.4Hz, 3.3Hz), 3.61(s,3H), 3.75-4.8(m,7H), 4.95-5.35(m,2H), 5.05-6.2(m,1H), 6.29(d,1H, J=3.6Hz), 6.59(d,1H, J=3.6)	81	fumarate 183-185 °C EtOH	301 271 233	n-BuOH K ₂ CO ₃	120°C 4h B

Ex. No.	Compound No.	¹ H-NMR data of free base (CDCl ₃) δ (ppm)	Yield of free base	Type of salt M.P. of acid addition salt Recrystallization solvent	UV of acid addition salt EtOH λ max (nm)	Reaction solvent Coexisting base	Reaction temp. Reaction time Reaction vessel
15	118	1.21 (t, 3H, J=7.0 Hz), 1.3-2.1 (m, 4H), 3.2-3.7 (m, 5H), 3.61 (s, 3H), 3.9-4.4 (m, 4H), 4.7 (br-t, 1H, J=6 Hz), 4.9-5.35 (m, 2H), 5.7-6.3 (m, 1H), 6.29 (d, 1H, J=3.6 Hz), 6.57 (d, 1H, J=3.6 Hz)	30	fumarate 163-165 °C EtOH	300 272 233	n-BuOH K ₂ CO ₃	120 °C 4h B
16	119	1.5-2.2 (m, 4H), 2.06 (s, 3H), 3.3-3.85 (m, 2H), 3.62 (s, 3H), 3.9-4.4 (m, 4H), 4.68 (br-t, 1H, J=6.2 Hz), 4.85-5.35 (m, 3H), 5.75-6.2 (m, 1H), 6.28 (d, 1H, J=3.7 Hz), 6.60 (d, 1H, J=3.7 Hz)	30	fumarate 164-166 °C i-PrOH	302 271 234	n-BuOH K ₂ CO ₃	120 °C 4h B
17	120	1.8-2.3 (m, 4H), 3.63 (s, 3H), 3.55-3.9 (m, 2H), 4.0-4.4 (m, 4H), 4.69 (br-t, 1H, J=6.2), 4.95-5.45 (m, 3H), 5.75-6.25 (m, 1H), 6.31 (d, 1H, J=3.7 Hz), 6.61 (d, 1H, J=3.7 Hz), 6.95-7.2 (m, 2H), 7.9-8.2 (m, 2H)	30	fumarate 159-164 °C EtOH	301 271 233 204	n-BuOH K ₂ CO ₃	120 °C 4h B
18	121	1.16 (t, 3H, J=7.3 Hz), 1.2-1.7 (m, 2H), 1.8-2.3 (m, 2H), 2.4-3.3 (m, 5H), 3.62 (s, 3H), 4.07 (t-like, 2H, J=5.7 Hz), 4.5-4.95 (m, 3H), 5.0-5.4 (m, 2H), 5.8-6.3 (m, 1H), 6.30 (d, 1H, J=3.6 Hz), 6.58 (d, 1H, J=3.6 Hz)	80	HCℓ·salt 185-200 °C i-PrOH	—	n-BuOH K ₂ CO ₃	120 °C 4h B

Ex. No.	Compound No.	¹ H-NMR data of free base (CDCl ₃) δ (ppm)	Yield of free base	Type of salt M.P. of acid addition salt Recrystallization solvent	UV of acid addition salt λ max (nm)	Reaction solvent Coexisting base	Reaction temp. Reaction time Reaction vessel
19	122	1.1-1.2 (m, 5H), 1.96 (s, 3H), 2.9-3.35 (m, 2H), 3.62 (s, 3H), 3.9-4.2 (t-like, 2H, J=6Hz), 4.5-4.8 (m, 3H), 5.0-5.4 (m, 2H), 5.4 (br, 1H), 5.8-6.3 (m, 1H), 6.28 (d, 1H, J=3.5Hz), 6.60 (d, 1H, J=3.5Hz)	77	HCℓ·salt 156-158 °C i-PrOH	—	n-BuOH K ₂ CO ₃	120 °C 4h B
20	123	1.2-2.7 (m, 7H), 2.30 (s, 6H), 2.8-3.2 (m, 2H), 3.62 (s, 3H), 4.08 (t-like, 2H, J=6Hz), 4.5-4.9 (m, 3H), 4.95-5.4 (m, 2H), 5.8-6.3 (m, 1H), 6.31 (d, 1H, J=3.5Hz), 6.59 (d, 1H, J=3.5Hz)	96	HCℓ·salt i-PrOH	—	n-BuOH K ₂ CO ₃	120 °C 6h B
21	124	3.63 (s, 3H), 3.6-4.0 (m, 8H), 4.08 (t-like, 2H, J=6Hz), 4.7 (br, 1H), 4.95-5.4 (m, 2H), 5.7-6.3 (m, 1H), 6.28 (d, 1H, J=3.5Hz), 6.61 (d, 1H, J=3.5Hz)	100	HCℓ·salt 159-161 °C i-PrOH	—	n-BuOH —	80 °C 14h B
22	125	2.6-2.8 (m, 4H), 3.62 (s, 3H), 4.0-4.3 (m, 3H), 4.8 (br, 1H, J=6Hz), 5.0-5.4 (m, 2H), 5.8-6.3 (m, 1H), 6.23 (d, 1H, J=3.5Hz), 6.61 (d, 1H, J=3.5Hz)	100	HCℓ·salt 174-176 °C i-PrOH	302 237 206	n-BuOH K ₂ CO ₃	120 °C 6h B

Ex. No.	Compound No.	¹ H-NMR data of free base. (CDC l ₃) δ (ppm)	Yield of free base	Type of salt M.P. of acid addition salt Recrystallization solvent	UV of acid addition salt λ max (nm)	Reaction solvent Coexisting base	Reaction temp. Reaction time Reaction vessel
23	126	2.33(s, 3H), 2.50(t, 4H, J=5Hz), 3.62(s, 3H), 3.91(t, 4H, J=5Hz), 4.08(t-like, 2H, J=6Hz), 4.7(br-t, 1H, J=7Hz), 4.95-5.4(m, 2H), 5.75-6.3(m, 1H), 6.30(d, 1H, J=3.7Hz), 6.50(d, 1H, J=3.7Hz)	100	HC l ₂ ·salt 190-195 °C i-PrOH	—	n-BuOH K ₂ CO ₃	100 °C 6h B
24	129	3.20(t, 4H, J=5Hz), 3.63(s, 3H), 3.8-4.1(m, 6H), 4.67(br-t, 1H, J=6Hz), 4.9-5.3(m, 2H), 5.75-6.1(m, 1H), 6.33(d, 1H, J=3.6Hz), 6.62(d, 1H, J=3.6Hz), 6.7-7.0(m, 4H)	89	HC l ₂ ·salt 190-194 °C EtOH	301 239 206	n-BuOH K ₂ CO ₃	120 °C 27h B
25	130	2.53(t, 4H, J=5Hz), 3.54(s, 2H), 3.61(s, 3H), 3.7-4.1(m, 6H), 4.6(br-t, 1H, J=6Hz), 4.85-5.3(m, 2H), 5.6-7.2(m, 1H), 6.27(d, 1H, J=3.5Hz), 6.57(d, 1H, J=3.5Hz), 7.0-7.3(m, 5H)	26	—	—	n-BuOH K ₂ CO ₃	120 °C 17h B
26	131	2.50(t, 4H, J=5Hz), 3.47(s, 2H), 3.60(s, 3H), 3.7-4.2(m, 6H), 4.69(br-t, 1H, J=6Hz), 4.9-5.4(m, 2H), 5.76-6.25(m, 1H), 6.26(d, 1H, J=3.5Hz), 6.56(d, 1H, J=3.5Hz), 6.8-7.45(m, 4H)	89	HC l ₂ ·salt 158-163 °C EtOH/n-hexane	302 236 206	n-BuOH K ₂ CO ₃	120 °C 18h B

Ex. No.	Com- pound No.	¹ H-NMR data of free base (CDC l ₃) δ (ppm)	Yield of free base	Type of salt M.P. of acid addition salt Recrystallization solvent	UV of acid addition salt EtOH λ max (nm)	Reaction solvent Coexisting base	Reaction temp. Reaction time Reaction vessel
27	132	2.4-2.8(m, 6H), 2.8-3.1(m, 2H), 3.62(s, 3. H), 3.7-4.2(m, 6H), 4.71(br-t, 1H, J=6), 4.9-5.4(m, 2H), 5.75-6.3(m, 1H), 6.31(d, 1H, J=3.7), 6.60(d, 1H, J=3.7), 7.2-7.7(m, 4H)	83	HC l ₂ ·salt 160-163 °C i-PrOH/EtOH	304 237 207	n-BuOH K ₂ CO ₃	120 °C 15h B
28	133	2.46(t-like, 4H, J=5Hz), 3.61(s, 3H), 3.75-4.15(m, 6H), 4.23 (s, 1H), 4.5-4.8(m, 1H), 4.95-5.4(m, 2H), 5.8-6.2(m, 1H), 6.23(d, 1H, J=3.5Hz), 6.56(d, 1H, J=3.5Hz), 7.1-6.9(m, 4H), 7.5-7.2(m, 4H)	77	HC l ₂ ·salt 166-169 °C i-PrOH	302 230 206	n-BuOH K ₂ CO ₃	120 °C 14h B
29	135	3.63(s, 6H), 3.9-4.25(m, 12H), 4.7(br-t, 2H, J=6Hz), 4.95-5.4(m, 4H), 5.8-6.3(m, 2H), 6.34(d, 2H, J=3.7Hz), 6.61(d, 2H, J=3.7Hz)	87	HC l ₂ ·salt 170-175 °C (dec)	—	n-BuOH K ₂ CO ₃	100 °C 24h B
30	136	2.46(t-like, 4H, J=5Hz), 3.09(s, 3H), 3.61(s, 3H), 3.87(t-like, 4H, J=5Hz), 4.15-4.4(m, 3H), 4.9-5.3(m, 2H), 5.6-6.1(m, 1H), 6.21(d, 1H, J=3.6Hz), 6.55(d, 1H, J=3.6Hz), 6.8-7.6(m, 8H)	58	HC l ₂ ·salt 155-161 °C i-PrOH	302 241 206	n-BuOH K ₂ CO ₃	120 °C 8h B

Ex. No.	Compound No.	¹ H-NMR data of free base (CDCl ₃) δ (ppm)	Yield of free base	Type of salt addition H.P. of acid Recrystallization solvent	UV of acid addition salt EtOH λ max (nm)	Reaction solvent Coexisting base	Reaction temp. Reaction time Reaction vessel
31	137	2.45 (t-like, 4H, J=5Hz), 3.60 (s, 3H), 3.85 (t-like, 4H, J=5Hz), 4.15-4.3 (m, 5H), 5.0-5.3 (m, 4H), 5.7-6.1 (m, 2H), 6.21 (d, 1H, J=4Hz), 6.55 (d, 1H, J=4Hz), 7.1-6.9 (m, 4H), 7.5-7.2 (m, 4H)	54	—	—	DMF K ₂ CO ₃	100 °C 5h B
32	138	1.4-2.3 (m, 4H), 2.08 (s, 3H), 2.38 (s, 3H), 3.5-3.85 (m, 2H), 3.73 (s, 3H), 4.0-4.4 (m, 2H), 4.66 (d, 2H, J=5.3Hz), 4.8-5.35 (m, 3H), 5.7-6.2 (m, 1H), 6.43 (d, 1H, J=3.6Hz), 6.89 (d, 1H, J=3.6)	30	fumarate — EtOH	—	n-BuOH K ₂ CO ₃	120 °C 4h B
33	139	2.03 (t-like, 4H, J=5Hz), 3.5-3.3 (m, 9H), 3.74 (s, 3H), 5.8 (br-s, 1H), 6.17 (d, 1H, J=3.6Hz), 6.51 (d, 1H, J=3.5Hz), 6.72 (d, 2H, J=9Hz), 7.3-6.9 (m, 17H)	60	—	—	n-BuOH K ₂ CO ₃	120 °C 5h B
34	140	0.90 (t, 3H, J=7Hz), 0.95 (t, 3H, J=7Hz), 1.4-2.04 (m, 4H), 2.46 (t-like, 4H, J=5Hz), 3.2-3.5 (m, 2H), 3.75-4.1 (m, 6H), 4.23 (s, 1H), 4.7 (br-s, 1H), 6.22 (d, 1H, J=4Hz), 6.59 (d, 1H, J=4Hz), 6.8-7.15 (m, 4H), 7.2-7.5 (m, 4H)	94	HC ₂ O ₄ salt 181-189 °C EtOH	—	n-BuOH K ₂ CO ₃	120 °C 24h B

Ex. No.	Compound No.	¹ H-NMR data of free base (CDC l ₃) δ (ppm)	Yield of free base	Type of salt H.P. of acid addition salt Recrystallization solvent	UV of acid addition salt EtOH λ max (nm)	Reaction solvent Coexisting base	Reaction temp. Reaction time Reaction vessel
35	141	0.89(t, 3H, J=7Hz), 1.55-2.05(m, 2H), 2.46(t-like, 4H, J=5Hz), 3.75-4.15(m, 8H), 4.23(s, 1H), 4.65(br-t, 1H), 4.95-5.4(m, 2H), 5.75-6.2(m, 1H), 6.23(d, 1H, J=4Hz), 6.60(d, 1H, J=4Hz), 6.85-7.15(m, 4H), 7.2-7.5(m, 4H)	64	HC l ₂ · salt 129-131 °C i-PrOH	—	DMF K ₂ CO ₃	100 °C 14h B
36	142	0.2-0.7(m, 4H), 0.9-1.4(m, 1H), 2.46(t-like, 4H, J=5Hz), 3.7-4.15(m, 8H), 4.23(s, 1H), 4.45-4.8(br-s, 1H), 4.95-5.4(m, 2H), 5.75-6.2(m, 1H), 6.25(d, 1H, J=4Hz), 6.73(d, 1H, J=4Hz), 6.85-7.15(m, 4H), 7.2-7.5(m, 4H)	65	HC l ₂ · salt 165-169 °C EtOH	—	DMF K ₂ CO ₃	100 °C 14h B
37	143	2.46(t-like, 4H, J=5Hz), 3.75-4.1(m, 6H), 4.24(s, 1H), 4.5-4.7(m, 3H), 4.95-5.35(m, 4H), 5.7-6.2(m, 2H), 6.26(d, 1H, J=4Hz), 6.59(d, 1H, J=4Hz), 6.9-7.1(m, 4H), 7.2-7.5(m, 4H)	97	HC l ₂ · salt 167-173 °C i-PrOH	—	DMF —	100 °C B
38	145	2.46(t-like, 4H, J=5Hz), 3.86(t-like, 4H, J=5Hz), 4.1-4.3(m, 5H), 4.6-4.75(m, 2H), 4.95-5.3(m, 6H), 5.7-6.2(m, 3H), 6.23(d, 1H, J=4Hz), 6.58(d, 1H, J=4Hz), 6.85-7.15(m, 4H), 7.2-7.5(m, 4H)	73	—	—	DMF K ₂ CO ₃	50 °C 10h B

Ex. No.	Compound No.	H-NMR data of free base, (CDCl ₃) δ (ppm)	Yield of free base	Type of salt M.P. of acid addition salt Recrystallization solvent	UV of acid addition salt λ max (nm)	Reaction solvent Cocatalyst base	Reaction temp. Reaction time Reaction vessel
39	146	2.46 (t-like, 4H, J=5Hz), 3.88 (t-like, 4H, J=5Hz), 4.03 (m, 2H), 4.23 (s, 1H), 4.7 (bs-s, 1H), 4.9-5.3 (m, 2H), 5.21 (s, 2H), 5.7-6.2 (m, 1H), 6.25 (d, 1H, J=3.6Hz), 6.55 (d, 1H, J=3.6Hz), 6.8-7.5 (m, 13H)	62	HC ℓ ·salt 187-190 °C EtOH	304 239 209	DMF K ₂ CO ₃	100 °C 6h B
40	148	0.1-0.5 (m, 4H), 1.0 (m, br, 1H), 1.60 (d, 3H, J=7Hz), 3.23 (2H, dd, J=7Hz, 7Hz), 3.60 (3Hz), 4.7 (br, 1H), 5.0 (br, 1H), 5.4 (m, 1H), 6.11 (d, 1H, J=3.5Hz), 6.52 (d, 1H, J=3.5Hz), 7.2-7.4 (m, 5H)	95	HC ℓ ·salt 118-119 °C acetone-diethylether	297 235 206	n-BuOH K ₂ CO ₃	130 °C 20h A
41	149	3.62 (s, 3H), 4.09 (t-2H, J=5.5Hz), 4.5-5.2 (br, 3H), 5.0-5.4 (m, 2H), 5.8-6.3 (m, 1H), 6.16 (d, 1H, J=3.5Hz), 6.58 (d, 1H, J=3.5Hz)	100	HC ℓ ·salt 215-223 °C (dec.) i-PrOH / (1-Pr) ₂ O	302 268 235 207	aq. ammonia —	110 °C 15h A
42	150	1.1-2.2 (m, 10H), 3.62 (s, 3H), 3.9-4.2 (m, 3H), 4.4-4.8 (m, 2H), 5.0-5.4 (m, 2H), 5.7-6.3 (m, 1H), 6.14 (d, 1H, J=3.4Hz), 6.56 (d, 1H, J=3.4Hz)	92	HC ℓ ·salt 187-189 °C i-PrOH	296 235	— K ₂ CO ₃	120 °C 19h A

Ex. No.	Compound No.	¹ H-NMR data of free base (CDC l ₃) δ (ppm)	Yield of free base	Type of salt M.P. of acid addition salt Recrystallization solvent	UV of acid addition salt EtOH λ max (nm)	Reaction solvent Coexisting base	Reaction temp. Reaction time Reaction vessel
43	151	3.63 (s, 3H), 4.0-4.3 (m, 4H), 4.7 (br, 2H), 4.95-5.4 (m, 4H), 5.8-6.3 (m, 2H), 6.18 (d, 1H, J=3.5Hz), 6.59 (d, 1H, J=3.5Hz)	76	—	—	n-BuOH	100 °C 18h B
44	152	2.28 (s, 6H), 2.55 (t, 2H, J=5.7Hz), 3.5-3.7 (m, 4H), 4.0-4.2 (m, 2H), 4.7 (br-s, 1H), 4.9-5.4 (m, 2H), 5.4 (br-s, 1H), 5.8-6.3 (m, 1H), 6.21 (d, 1H, J=3.5Hz), 6.56 (d, 1H, J=3.5Hz)	93	HC l · salt 199-212 °C (dec.) EtOH	297 234	— K ₂ CO ₃	110 °C 15h B
45	153	1.4-1.8 (m, 4H), 2.3-2.7 (m, 6H), 3.62 (s, 3H), 3.5-3.7 (m, 2H), 4.10 (m, 2H), 4.6 (m, 1H), 5.0-5.4 (m, 2H), 5.8-6.2 (m, 1H), 6.21 (d, 1H, J=3.5Hz), 6.56 (d, 1H, J=3.5Hz)	93	HC l · salt 210-220 °C (dec.) EtOH	297 234	— K ₂ CO ₃	130 °C 3h B
46	154	2.4-2.7 (m, 6H), 3.63 (s, 3H), 3.5-3.8 (m, 6H), 4.10 (br-t, 2H, J=6Hz), 4.8-5.5 (m, 4H), 5.6-6.2 (m, 1H), 6.20 (d, 1H, J=3.5Hz), 6.58 (d, 1H, J=3.5Hz)	60	HC l · salt 205-212 °C (dec.) EtOH	296 234	— K ₂ CO ₃	130 °C B
47	155	3.63 (s, 3H), 4.10 (t, 2H, J=5.5Hz), 4.6-4.85 (m, 3H), 4.9-5.4 (m, 3H), 5.7-6.3 (m, 1H), 6.12 (d, 1H, J=3.5Hz), 6.56 (d, 1H, J=3.5Hz), 7.2-7.5 (m, 5H)	94	HC l · salt 174-178 °C acetone	295 235 208	— K ₂ CO ₃	130 °C 5h B

Ex. No.	Compound No.	¹ H-NMR data of free base (CDCl ₃) δ (ppm)	Yield of free base	Type of salt M.P. of acid addition salt Recrystallization solvent	UV of acid addition salt λ max (nm)	Reaction solvent Coexisting base	Reaction temp. Reaction time Reaction vessel
48	160	1.82(s, 6H), 3.58(s, 3H), 3.67(t, 2H, J=5.3Hz), 4.5(br-t, 1H, J=5.5Hz), 4.85-5.2(m, 2H), 5.5-5.95(m, 1H), 4.06(d, 1H, J=3.5Hz), 6.53(d, 1H, J=3.5Hz), 7.1-7.6(m, 5H)	91	HCℓ·salt 181-200 °C acetone	297 269 234 207	n-BuOH K ₂ CO ₃	180 °C 16h A
49	161	1.75(d, 3H, J=6.6Hz), 3.59(s, 3H), 4.01(br-t, 2H, J=5.2Hz), 4.7(br-t, 1H, J=5.2Hz), 4.9-5.35(m, 3H), 5.7-6.2(m, 1H), 6.0(d, 1H, J=3.5Hz), 6.2(t, 1H, J=7Hz), 6.48(d, 1H, J=3.5Hz), 7.3-8.3(m, 7H)	70	HCℓ·salt 135-140 °C i-PrOH	294 223	— K ₂ CO ₃	150 °C 6h B
50	162	1.7-2.3(m, 4H), 2.83(br-t, 2H, J=6Hz), 3.64(s, 3H), 4.11(br-t, 2H, J=6Hz), 4.7(br-t, 1H, J=6Hz), 4.8-5.4(m, 2H), 5.5(m, 1H), 5.8-6.4(m, 1H), 6.09(d, 1H, J=3.6Hz), 6.56(d, 1H, J=3.6Hz), 7.0-7.5(m, 4H)	79	HCℓ·salt 196-200 °C (dec.) i-PrOH	297 235 207	— K ₂ CO ₃	130 °C 6h B
51	163	3.60(s, 3H), 3.96(t, 3H, J=6Hz), 4.65(br-t, 1H, J=6Hz), 4.9-5.35(m, 3H), 5.65-6.1(m, 1H), 6.12(d, 1H, J=3.5Hz), 6.50(s, 1H), 6.54(d, 1H, J=3.5Hz), 7.2-7.4(m, 10H)	45	HCℓ·salt 183-185 °C i-PrOH	298 236 208	— K ₂ CO ₃	150 °C 27h B

Ex. No.	Compound No.	¹ H-NMR data of free base (CDC l ₂) δ (ppm)	Yield of free base	Type of salt M.P. of acid Recrystallization solvent	UV of acid addition salt EtOH λ max (nm)	Reaction solvent Coexisting base	Reaction temp. Reaction time Reaction vessel
52	164	2.95(t, 2H, J=6.8Hz), 3.62(s, 3H), 3.6-3.95(m, 2H), 4.0-4.2(m, 2H), 4.5-4.9(m, 2H), 4.95-5.4(m, 2H), 5.8-6.3(m, 1H), 6.09(d, 1H, J=3.5Hz), 6.55(d, 1H, J=3.5Hz), 7.2-7.4(m, 5H)	100	HC l ₂ · salt 152-153 °C i-PrOH	295 234 207	— K ₂ CO ₃	130 °C 1.5h B
53	165	3.29(s, 6H), 3.62(s, 3H), 4.0-4.2(m, 2H), 4.6(br-s, 1H), 5.0-5.4(m, 2H), 5.8-6.3(m, 1H), 6.38(d, 1H, J=3.5Hz), 6.50(d, 1H, J=3.5Hz)	50	HC l ₂ · salt 175-180 °C EtOH	299 236 202	n-BuOH K ₂ CO ₃	120 °C 14h A
54	166	3.26(s, 3H), 3.62(s, 3H), 4.07(t-like, 2H, J=6Hz), 4.7(br, 1H), 4.96(s, 2H), 4.9-5.4(m, 2H), 5.75-6.3(m, 1H), 6.26(d, 1H, J=3.6Hz), 6.53(d, 1H, J=3.6Hz), 7.2-7.4(m, 5H)	99	fumarate 163-164 °C EtOH	—	n-BuOH	100 °C B
55	167	2.97(dd, 2H, J=7.5, J=9.9Hz), 3.22(s, 3H), 3.63(s, 3H), 3.88(dd, 2H, J=7.5, J=9.9Hz), 4.1(m, 2H), 4.6(br-t, 1H, J=6Hz), 4.95-5.4(m, 2H), 5.8-6.3(m, 1H), 6.35(d, 1H, J=3.5Hz), 6.57(d, 1H, J=3.5Hz), 7.1-7.4(m, 5H)	74	HC l ₂ · salt 177-183 °C i-PrOH	299 236 207	— K ₂ CO ₃	140 °C 14h B

Ex. No.	Compound No.	¹ H-NMR data of free base : (CDCl ₃) δ (ppm)	Yield of free base	Type of salt M.P. of acid addition salt Recrystallization solvent	UV of acid addition salt EtOH λ max (nm)	Reaction solvent Coexisting base	Reaction temp. Reaction time Reaction vessel
56	168	1.09 (t, 3H, J=7Hz), 1.63 (d, 3H, J=7Hz), 3.3-3.7 (m, 2H), 3.62 (s, 3H), 4.07 (dd, 2H, J=5.5Hz, 5.5Hz), 4.7 (br-t, like, 1H), 5.0-5.3 (m, 2H), 5.8-6.2 (m, 1H), 6.25 (d, 1H, J=3.5Hz), 6.50 (d, 1H, J=7Hz), 6.56 (d, 1H, J=3.5Hz), 7.2-7.4 (m, 5H)	49	—	—	K ₂ CO ₃ LiI	150 °C 40h A
57	169	1.60 (3H, d, J=7Hz), 1.75 (3Hz), 3.59 (s, 3H), 4.7 (s, br, 1H), 3.97 (d, 2H, J=6Hz), 4.8 (s, 1H), 4.9 (s, 1H), 5.1 (s, br, 1H), 5.4 (m, 1H), 6.11 (d, 1H, J=3.5Hz), 6.52 (d, 1H, J=3.5Hz), 7.2-7.4 (m, 5H)	80	HCℓ·salt 160-164 °C acetone	296 235 206	n-BuOH K ₂ CO ₃	130 °C 15h A
58	171	3.29 (s, 6H), 4.07 (t-like, 2H, J=6Hz), 4.64 (d, 2H, J=5.5Hz), 4.9-5.4 (m, 4H), 5.7-6.2 (m, 2H), 6.41 (d, 1H, J=3.5Hz), 6.59 (d, 1H, J=3.5Hz)	74	HCℓ·salt 110-111 °C EtOH	299 237 207	n-BuOH K ₂ CO ₃	120 °C 16h B

Wherein, i-PrOH: isopropylalcohol; n-BuOH: N-butylalcohol; EtOH: ethylalcohol; (i-Pr)₂O: diisopropylether

Example 59: Effect on Partial Pressure Value of Gases in Arterial Blood (Injection system)

(Method A)

Male Wister strain rats (body weight about 300 g) were anesthetized intra-peritoneally with urethane.

and a cannula was inserted into the respiratory tract and the femoral artery, respectively. A suspension (30-100 μ m, 10 mg/ml) of carbon powder in a corn oil was intratracheally injected to induce a hypoxemia state (PaO_2 : 50-60 mmHg). A compound in accordance with the present invention was intravenously injected into these hypoxemia model animals by a continuous manner (0.1 mg/kg/min., 10 min), and then a partial pressure value of gases (PaO_2 , PaCO_2) in arterial blood were immediately determined.

(Method B)

Male Wister strain rats (body about 300 g) were anesthetized with halothane inhalant, and then 2.0% acetic acid was intratracheally injected at 0.6 ml/kg to induce a respiratory insufficiency. The animals were intra-peritoneally anesthetized with urethane- α -chloralose, and a cannula was inserted into the femoral artery. After the hypoxemic state (PaO_2 : 60-70 mmHg) was observed a compound in accordance with the present invention (test substance) was intravenously injected into these hypoxemia model animals by a continuous manner (0.1 mg/kg/min), and then a partial pressure value of gases (PaO_2 , PaCO_2) in arterial blood were immediately determined.

The results are as shown in Table 1 below.

Table 1

Activity for Increasing PaO_2 and Decreasing PaCO_2 by Intravenous Injection			
Test Compound	Method	Activity for Increasing PaO_2 ΔPaO_2	Activity for Decreasing PaCO_2 ΔPaCO_2
119	A	+7.1	-2.6
124	B	+5.7	-4.0
133	A	+6.9	-0.6
143	A	+5.0	+1.1
150	B	+18.4	-18.6
156	B	+19.7	-9.1
162	B	+18.1	-17.2
164	B	+15.4	-19.2
165	B	+7.9	+1.1
167	B	+11.3	-6.6
Unit: mmHg (Indication of activity) ΔPaO_2 = (PaO_2 after administration - PaO_2 before administration) for test compound ΔPaCO_2 = (PaCO_2 after administration - PaCO_2 before administration) for test compound			

Example 60: Effect on Partial Pressure Value of Gases in Arterial Blood (Oral Administration System)

Male Wistar strain rats (body weight about 250 g) fasted overnight were anesthetized with halothane inhalant, and then a cannula was inserted into the femoral artery. After the animals recovered from the anesthesia, they were again anesthetized with halothane inhalant, and then 2.0% acetic acid was intratracheally injected at 0.8 ml/kg to induce a hypoxemia state. After the hypoxemic state was observed over about 60 min., a compound in accordance with the present invention (test substance) was orally administered to the animals. On 60 min. after the administration, the partial pressure value of gases (PaO_2 , PaCO_2) in arterial blood were determined.

The results are as shown in Table 2 below.

Table 2

Activity for Increasing PaO₂ and
Decreasing PaCO₂ by Intravenous Injection

Test Compound	Activity for Increasing PaO ₂ Δ PaO ₂	Activity for Decreasing PaCO ₂ Δ PaCO ₂
124	+	+
156	+ +	+
165	+	±

(Indication of activity)

Δ PaO₂ = (PaO₂ after administration - PaO₂ before administration) for test compound

Δ PaCO₂ = (PaCO₂ after administration - PaCO₂ before administration) for test compound

Δ PaO₂ +: +3 - +6 mmHg

 ++: +6 - +9 mmHg

Δ PaCO₂ ±: 0 - -3 mmHg

 +: -3 - -6 mmHg

 ++: -6 - -9 mmHg

Example 61: Preparation of Tablet

A tablet containing 30 mg of the compound prepared in Example 1 was prepared as follows:

Compound prepared in Ex. 1	30 mg
Lactose	87 mg
Starch	30 mg
Magnesium stearate	3 mg

Example 62: Preparation of Injection

A solution for injection containing 0.3 mg, based on 1 ml of the solution, of the compound prepared in Example 1 was prepared according to the following formulation.

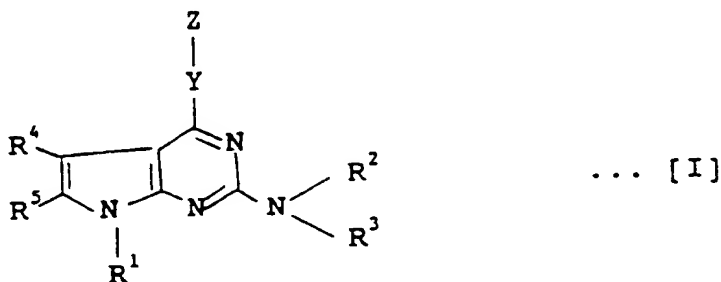
Compound prepared in Ex. 1	30 mg
Sodium chloride	900 mg
Distilled water for injection	100 ml

INDUSTRIAL APPLICABILITY

The compounds in accordance with the present invention, and pharmaceutical preparations thereof, are particularly useful for the treatment of hypoxemia associated with respiratory diseases, and further, an effective process for producing same is provided.

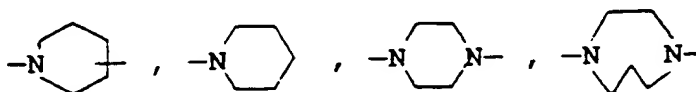
Claims

1. A pyrrolo[2,3-d]pyrimidine derivative represented by the general formula [I]:



wherein

- R¹ represents a hydrogen atom, or an unsubstituted or substituted alkyl, alkenyl or aralkyl group;
 R² and R³ independently of each other, represent a hydrogen atom, or an unsubstituted or substituted alkyl, alkenyl, aralkyl or alkylcarbonyl group; or R² and R³ are optionally taken together with the adjacent nitrogen atom to form a cyclic amino group;
 R⁴ and R⁵ independently of each other, represent a hydrogen atom, halogen atom, or an unsubstituted or substituted alkyl group;
 Y is a linking group bonded to the pyrimidine ring via a nitrogen atom therein of the formula:



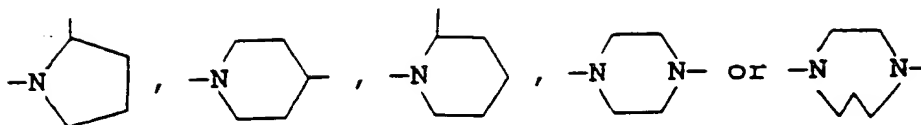
or -N(G)-, wherein G represents a hydrogen atom or an alkyl group;

Z represents a group bonded to a carbon or nitrogen atom in the linking group, and is a hydrogen atom, an unsubstituted or substituted alkyl, alkenyl, aralkyl, aryl, alkylcarbonyl, arylcarbonyl or aralkylcarbonyl group; or represents a group bonded to a carbon atom in the linking group, and is a carboxyl, hydroxyl group; or an unsubstituted or substituted alkyloxycarbonyl, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkyloxy or alkyloxyiminoalkyl group, or mono- or disubstituted alkyl- and/or alkylcarbonylamino group; or Y and Z are taken together to form morpholino or thiomorpholino group;

each substituent in said substituted group is substituted at a chain or cyclic moiety of the alkyl, alkenyl, aralkyl or aryl moiety, respectively, and represents an alkyl, halogenated alkyl, alkylcarbonyl, alkyloxy, alkylcarbonyloxy, hydroxyl, mono- or dialkylamino, amino, morpholino, piperidino, nitro or cyano group, or a halogen atom;

with a proviso that R² and R³ do not represent a hydrogen atom at the same time, and that when R¹ represents hydrogen atom, the combinations wherein one of R² and R³ represents a hydrogen atom and another represents an alkyl group are excluded; and
 a pharmaceutically acceptable acid addition salt.

2. A pyrrolo[2,3-d]pyrimidine derivative and a pharmaceutically acceptable acid addition salt thereof in accordance with claim 1, wherein Y is a linking group having the formula:



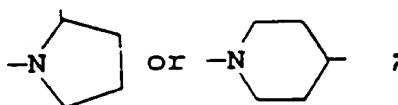
3. A pyrrolo[2,3-d]pyrimidine derivative and a pharmaceutically acceptable acid addition salt thereof in accordance with claim 1, wherein Y is a group -N(G)-, and G is a hydrogen atom, methyl group or ethyl group.

4. A pyrrolo[2,3-d]pyrimidine derivative and a pharmaceutically acceptable acid addition salt thereof in accordance with claim 1, wherein R¹ is a lower alkyl group or allyl group.

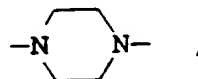
5. A pyrrolo[2,3-d]pyrimidine derivative and a pharmaceutically acceptable acid addition salt thereof in accordance with claim 1, wherein R² is a hydrogen atom, R³ is an alkyl group, allyl group or 2-methylallyl group.

6. A pyrrolo[2,3-d]pyrimidine derivative and a pharmaceutically acceptable acid addition salt thereof in accordance with claim 1, wherein R⁴ and R⁵ are a hydrogen atom.

7. A pyrrolo[2,3-d]pyrimidine derivative and a pharmaceutically acceptable acid addition salt thereof in accordance with Claim 1, wherein R¹ is methyl group or allyl group; R² is a hydrogen atom; R³ is cyclopropylmethyl group; allyl group or 2-methylallyl group; R⁴ and R⁵ are a hydrogen atom; Y is a linking group having the formula:

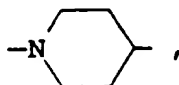


and Z is a hydrogen atom, alkyl group, alkylcarbonyl group, alkyloxycarbonyl group or alkylcarbonyloxy group; or Y is a linking group having the formula:

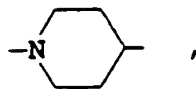


and Z is an alkyl group, or an unsubstituted or substituted aralkyl group; or Y is a linking group having the formula: -N(G)-, G is a hydrogen atom or alkyl group, and Z is cyclohexyl group, allyl group, an aralkyl group which may be substituted by one to three methyl groups on the alkyl chain; or Y and Z taken together is a morpholino group.

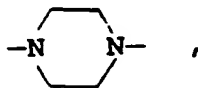
8. A pyrrolo[2,3-d]pyrimidine derivative and a pharmaceutically acceptable acid addition salt thereof in accordance with claim 1, wherein R¹ is a methyl group or allyl group; R² is a hydrogen atom; R³ is a cyclopropylmethyl group, allyl group or 2-methylallyl group; Y is a linking group having the formula:



and Z is a hydrogen atom; or Y is a linking group having the formula:

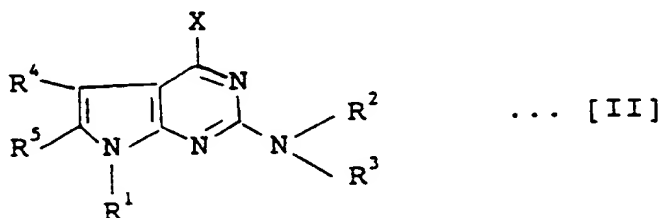


and Z is a hydrogen atom, isopropoxy carbonyl group or acetyloxy group; or Y is a linking group having the formula:



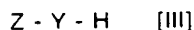
and Z is a methyl group or bis(4-fluorophenyl) methyl group; or Y is a linking group having the formula: -NH-, and Z is cyclohexyl group, allyl group, benzyl group, 1-phenylethyl group, 1-methyl-1-phenylethyl group, 2-phenylethyl group, 1-(1-naphthyl) ethyl group or 1,2,3,4-tetrahydronaphthalene-1-yl group; or Y is a linking group having the formula: -N(CH₃)-, and Z is methyl group, benzyl group or phenethyl group.

9. A process for producing a pyrrolo[2,3-d]pyrimidine derivative and a pharmaceutically acceptable acid addition salt in accordance with claim 1, characterized by reacting a halogenated pyrrolo[2,3-d]-pyrimidine derivative or an acid addition salt thereof having the general formula [II]



wherein R¹, R², R³, R⁴ and R⁵ have the same definitions as those of the formula [I] in claim 1, X is a halogen atom;

with an amine compound having the general formula [III]



wherein Y and Z have the same definitions as those of said formula [I]; and further, mixing with an inorganic acid or organic acid, if necessary.

10. A pharmaceutical preparation comprising a pyrrolo[2,3-d]pyrimidine derivative in accordance with claim 1, as an efficacious ingredient.

11. A pharmaceutical preparation in accordance with claim 10, being efficacious for a treatment of hypoxemia.

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP90/01200

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int. Cl ⁵	C07D487/04, 519/00, A61K31/505, 31/535, 31/54, 31/55	
II. FIELDS SEARCHED		
Minimum Documentation Searched *		
Classification System *	Classification Symbols	
IPC	C07D487/04, 519/00, A61K31/505, 31/535, 31/54, 31/55	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *		
Chemical Abstracts	1967 - 1990	
III. DOCUMENTS CONSIDERED TO BE RELEVANT *		
Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages **	Relevant to Claim No. **
A	JP, A, 63-275598 (Beringer Mannheim GmbH), November 14, 1988 (14. 11. 88), Claim & EP, A, 286028 & DE, A, 3739366 & AU, A, 1439888 & HU, A, 46703	1-8
A	J. Heterocyclic Chem., 25 (6), p. 1893~1898 (1988), Kandasamy Ramasamy et al. "A Facile and Improved Synthesis of Tubercidin and Certain Related Pyrrolo 2,3-d pyrimidine Nucleosides by the Stereospecific Sodium Salt Glycosylation Procedure [I]"	1-8
A	J. Heterocyclic Chem., 24 (2), p. 425-30 (1987), Kurt Eger et al. "Selected Reactions on the O-Aminonitrile System of Substituted Pyrroles [I]"	1-9
<p>* Special categories of cited documents: **</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"S" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
December 7, 1990 (07. 12. 90)	December 25, 1990 (25. 12. 90)	
International Searching Authority	Signature of Authorized Officer	
Japanese Patent Office		

Form PCT/ISA/210 (second sheet) (January 1985)